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(54) Fused pyrimidine derivatives, process and intermediates for their preparation and pharmaceutical compositions containing them.

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DE-A- 1 795 722
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GB-A- 1 543 874

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Descriptl n

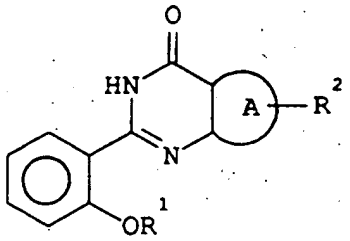
The present invention relates to fused pyrimidine derivatives, processes for their preparation, intermediates in their preparation, their use as therapeutic agents and to pharmaceutical compositions containing them. The compounds of this invention are inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase and are of use in combating such conditions where such inhibition is thought to be beneficial. They are bronchodilators and are therefore of use in combating chronic reversible obstructive lung diseases such as asthma and bronchitis. Some of the compounds of the present invention have anti-allergic activity and are therefore useful in combating allergic diseases such as allergic asthma, allergic rhinitis, urticaria and irritable bowel syndrome. Furthermore the compounds of this invention are vasodilators and are therefore of value in combating angina, hypertension and congestive heart failure.

GB-A-1,543,874 (Carlo Erba) discloses a series of substituted phenyl-3,4-dihydro-4-oxo-quinazoline derivatives which are said to possess anti-allergic activity.

FR-A-2,225,166 (Pfizer) discloses bicyclic and tricyclic ring systems containing a pyrimidine moiety as anti-allergic agents.

DE-A-1,795,722 (Karl Thomae) discloses substituted pyrimido[5,4-d]pyrimidines which act as cardiovascular agents.

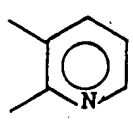
Accordingly, the present invention provides compounds of the formula (1):



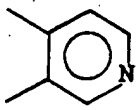
(1)

and pharmaceutically acceptable salts thereof, wherein

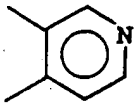
is a ring of sub-formula (a), (b), (c), (d), (e), (f) or (g) :



(a)



(b)



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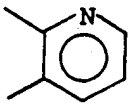

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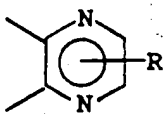

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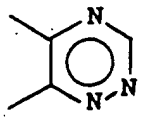

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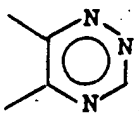

(g)

R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups;

R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_{1-6}alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5}cycloalkyl or C_{1-6}alkyl which is optionally substituted by $-CF_3$, phenyl, $-S(O)_nC_{1-6}$-alkyl wherein n is 0, 1 or 2, $-OR^6$, $-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_nC_{1-6}$alkyl, $-OR^6$ or $-NR^8R^9$ groups; and

R is hydrogen and can also be hydroxy when R^2 is hydroxy.

Suitably R^1 is C_{2-5}alkyl for example ethyl, n-propyl, isopropyl, butyl, isobutyl or pentyl.

Suitably R^1 is C_{3-5}alkenyl for example propenyl, butenyl or pentenyl.

Suitably R^1 is cyclopropylmethyl.

Examples of C_{1-6}alkyl substituted by 1 to 6 fluoro groups include $-CF_3$, $-CH_2CF_3$ or $-CF_2CHFCF_3$.

Preferably R^1 is n-propyl.

Suitably R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl or C_{1-6}alkoxy for example methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, methoxy, ethoxy or propoxy.

Suitably R^2 is hydroxy, hydrogen or hydrazino.

Suitably R^2 is phenyl or C_{1-6}alkyl for example methyl, ethyl or propyl.

Suitably R^2 is $-NHCOR^3$ for example formamido or acetamido.

Suitably R^2 is $-NR^4R^5$ for example amino, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, cyclopropylamino, morpholino, 2,2,2-trifluoroethylamino, phenethylamino, 3-methylthiopropylamino, 3-methylsulphinylpropylamino, 3-methylsulphonylpropylamino, 2-hydroxyethylamino, 3-hydroxypropylamino, 2-hydroxypropylamino, 3-methoxypropylamino, N-ethyl-N-(2-hydroxyethyl)amino, 2-aminoethylamino, 2-dimethylaminoethylamino, ethoxycarbonylmethylamino, carboxymethylamino, 2-ethoxycarbonylethylamino or 2-carboxyethylamino.

Suitably

is a group of sub-formula (a) thus forming a pyrido[2,3-d]pyrimidine ring system.

Suitably

is a group of sub-formula (b) thus forming a pyrido[3,4-d]pyrimidine ring system.

Suitably

is a group of sub-formula (c) thus forming a pyrido[4,3-d]pyrimidine ring system.

Suitably

is a group of sub-formula (d) thus forming a pyrido[3,2-d]pyrimidine ring system.

Suitably

is a group of sub-formula (e) thus forming a pteridine ring system.

Suitably

is a group of sub-formula (f) thus forming a pyrimido[5,4-e][1,2,4]triazine ring system.

Suitably

is a group of sub-formula (g) thus forming a pyrimido[4,5-e][1,2,4]triazine ring system.

Particular compounds of this invention are :

2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,4-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[4,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,2-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4,6(3H,5H)-dione,
2-(2-propoxyphenyl)pteridin-4,6,7(3H,5H,8H)-trione,
5,6-dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-amino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylamino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methoxy-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-amino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methoxy-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,